

AFT 24 ANDT

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Claims (Amended)What is claimed is:

1. A pharmaceutical formulation selected from the group consisting of:
  - 5 (a) a liquid aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody in a buffered solution, said formulation having a pH between about 4 and 8 and having a shelf life of at least 18 months;
  - 10 (b) an aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody in a buffered solution, said formulation having a pH between about 4 and 8 and having a shelf life of at least 18 months in the liquid state;
  - 15 (c) a liquid aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody in a buffered solution, said formulation having a pH between about 4 and 8 which maintains stability following at least 3 freeze/thaw cycles of the formulation; and
  - 20 (d) a liquid aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody in a buffered solution, said formulation having a pH between 4 and 8 and having enhanced stability of at least 12 months at a temperature of 2 - 8°C.
- 25 2. The formulation of claim 1, wherein the antibody is directed to TNF $\alpha$ .
3. The formulation of claim 1, wherein the concentration of the antibody is between about 1-150 mg/ml.
- 30 4. The formulation of claim 1, wherein the concentration of the antibody is about 50 mg/ml.
5. The formulation of claim 1, which further is suitable for single use subcutaneous injection.
- 35 6. The formulation of claim 1, wherein the antibody is <sup>a human</sup>an antibody, or an antigen-binding portion thereof, that dissociates from human TNF $\alpha$  with a K<sub>d</sub> of 1 x 10<sup>-</sup>

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8 M or less and a  $K_{\text{off}}$  rate constant of  $1 \times 10^{-3} \text{ s}^{-1}$  or less, both determined by surface plasmon resonance, and neutralizes human  $\text{TNF}\alpha$  cytotoxicity in a standard *in vitro* L929 assay with an  $\text{IC}_{50}$  of  $1 \times 10^{-7} \text{ M}$  or less.

5           7.       The formulation of claim 6, wherein the antibody, or antigen-binding portion thereof, is a recombinant antibody, or antigen-binding portion thereof.

10           8.       The formulation of claim 1, wherein the antibody is <sup>a human</sup> ~~an~~ the antibody, or antigen-binding portion, thereof ~~which~~ with the following characteristics:

a) dissociates from human  $\text{TNF}\alpha$  with a  $K_{\text{off}}$  rate constant of  $1 \times 10^{-3} \text{ s}^{-1}$  or less, as determined by surface plasmon resonance;

15           b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;

20           c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

25           9.       The formulation of claim 1, wherein the antibody, or antigen-binding portion thereof, has a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2.

30           10.      The formulation of claim 1, wherein the antibody, or antigen-binding portion thereof, neutralizes the activity of human  $\text{TNF}\alpha$ , chimpanzee  $\text{TNF}\alpha$  and at least one additional primate  $\text{TNF}\alpha$  selected from the group consisting of baboon  $\text{TNF}\alpha$ , marmoset  $\text{TNF}\alpha$ , cynomolgus  $\text{TNF}\alpha$  and rhesus  $\text{TNF}\alpha$ .

35           11.      The formulation of claim 1, wherein the antibody, or an antigen-binding portion thereof, also neutralizes the activity of mouse  $\text{TNF}\alpha$  and/or pig  $\text{TNF}\alpha$ .

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12. The formulation of claim 1, wherein the antibody, or antigen-binding portion thereof, binds human TNF $\alpha$  and is the antibody D2E7 or an antigen binding portion thereof.

5 13. An aqueous pharmaceutical composition comprising a polyol, a surfactant, and a buffer system comprising citrate and/or phosphate with a pH of about 4 to 8, in amounts sufficient to formulate an antibody for therapeutic use at a concentration of greater than about 45 mg/ml.

10 14. The composition of claim 13, wherein the polyol is mannitol and the surfactant is polysorbate 80.

15 15. The composition of claim 14, which contains 5-20 mg/ml of mannitol and 0.1-10 mg/ml of polysorbate 80.

20 16. The formulation of claim 13, which contains an antibody, or antigen-binding portion thereof, which binds human TNF $\alpha$  and is the antibody D2E7 or an antigen binding portion thereof.

25 17. A liquid aqueous pharmaceutical formulation comprising  
(a) 1-150 mg/ml of antibody,  
(b) 5-20 mg/ml of mannitol,  
(c) 0.1-10 mg/ml of Tween-80, and  
(d) a buffer system comprising citrate and/or phosphate, with a pH of 4 to 8.

30 18. The formulation of claim 17, wherein the pH is selected from the group consisting of between about 4.5 to about 6.0, between about 4.8 to about 5.5, and between about 5.0 to about 5.2.

35 19. The liquid aqueous pharmaceutical formulation of claim 17, which contains

- (a) about 50 mg/ml of antibody,  
(b) about 12 mg/ml of mannitol,  
(c) about 1 mg/ml of Tween-80, and

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(d) a buffer system comprising citrate and/or phosphate with a pH of about 4 to about 8.

- 5           20.    The formulation of claim 17, wherein the buffer system comprises
- (a) about 1.3 mg/ml of citric acid,
- (b) about 0.3 mg/ml of sodium citrate,
- (c) about 1.5 mg/ml of disodium phosphate dihydrate,
- 10           (d) about 0.9 mg/ml of sodium dihydrogen phosphate dihydrate, and
- (e) about 6.2 mg/ml of sodium chloride.
21.    The formulation of claim 19, wherein the antibody is directed to TNF $\alpha$ .
- 15           22.    The formulation of claim 19, wherein the antibody, or antigen-binding portion thereof, binds human TNF $\alpha$  and is the antibody D2E7 or an antigen binding portion thereof.
- 20           23.    The formulation of claim 22, which is administered to a subject suffering from a disorder in which TNF $\alpha$  activity is detrimental such that TNF $\alpha$  activity in the subject is inhibited.
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